


Predictive Factors for Intensive Care Unit Admission After Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy in Patients with Peritoneal Disease: A Single Center Retrospective Review

Fatores Preditivos para Admissão em Unidades de Cuidados Intensivos Após Cirurgia de Citorredução com Quimioterapia Intraperitoneal Hipertérmica em Doentes com Doença Peritoneal: Revisão Retrospectiva de um Centro

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ABSTRACT

Introduction: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) is a locoregional surgical therapy applied in patients with peritoneal-only metastatic disease of primary abdominal malignancies and is associated with increased overall survival. Our goal was to evaluate short-term outcomes after CRS+HIPEC regarding surgical morbidity, as well as to identify factors associated with selective Intensive Care Unit (ICU) admission and to assess the safety of managing these patients outside of the ICU.

Methods: A unicentric, retrospective, observational study of patients submitted to CRS+HIPEC between January 2016 and December 2020 at Instituto Português de Oncologia do Porto (IPO-Porto), was performed.

Results: During this period, 259 surgeries were performed. The majority of patients (68.7%) had no complications, 22.8% had CT-CAE 1/2 complications, 7.7% had CT-CAE 3/4 and 0.8% (n=2) died in the first 30 days postoperative (CT-CAE 5). Thirty-four percent (n=87) of patients were admitted to the ICU for postoperative surveillance (<48 hours). Patients who were not admitted to ICU demonstrated similar overall morbidity to the patients admitted to ICU for <48 hours. Predictive factors for ICU admission ($p<0.05$) were PCI>13, intraoperative blood loss>200 mL and cisplatin as the cytostatic agent.

Conclusion: Admittance to the ICU should not be standardized for every patient after CRS+HIPEC but rather stratified according to the complexity of surgical debulking.

Keywords: Cytoreduction Surgical Procedures; Hyperthermic Intraperitoneal Chemotherapy; Peritoneal Neoplasms; Postoperative Complications

RESUMO

Introdução: A cirurgia citorrredutora com quimioterapia intraperitoneal hipertérmica (CRS+HIPEC) é uma terapêutica cirúrgica locoregional realizada em doentes com doença metastática exclusivamente peritoneal de neoplasias abdominais primárias, e está associada a um aumento da sobrevida global. O objetivo foi avaliar os resultados a curto prazo após este procedimento no que concerne a morbidade cirúrgica, bem como identificar fatores associados à admissão seletiva em Unidade de Cuidados Intensivos (UCI) e avaliar a segurança desta abordagem.

Métodos: Foi realizado um estudo observacional, retrospectivo e unicêntrico dos doentes submetidos a CRS+HIPEC no Instituto Português de Oncologia do Porto (IPO-Porto) entre janeiro de 2016 e dezembro de 2020.

Resultados: Durante este período, foram realizadas 259 cirurgias. A maioria dos doentes (68,7%) não apresentou complicações, 22,8% apresentaram complicações CT-CAE 1/2, 7,7% apresentaram CT-CAE 3/4 e 0,8% (n=2) faleceram nos primeiros 30 dias de pós-operatório (CT-CAE 5). Trinta e quatro por cento (n=87) dos doentes foram admitidos na UCI para vigilância pós-operatória (<48 horas). Os doentes que não foram admitidos na UCI demonstraram morbidade global semelhante aos admitidos na UCI por <48 horas. Os fatores preditivos para admissão na UCI ($p<0,05$) foram PCI>13, perda sanguínea intraoperatória>200 mL e cisplatina como agente citostático.

Conclusão: A admissão na UCI não deve ser padronizada para todos os doentes após CRS+HIPEC, mas sim estratificada de acordo com a complexidade da citorredução cirúrgica.

Palavras-Chave: Complicações Pós-Operatórias; Neoplasias Peritoneais; Procedimentos Cirúrgicos de Citorredução; Quimioterapia Intraperitoneal Hipertérmica; Unidade de Cuidados Intensivos

INTRODUCTION

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) have been included in the treatment strategy of selected patients with peritoneal surface malignancies, both primary peritoneal cancers and peritoneal metastasis secondary to intra-abdominal malignancies.¹⁻³ This multimodal strategy combines surgical cytoreduction, including standard peritonectomy procedures

and multi-visceral resections, with the administration of HIPEC. The surgical component aims to remove all or nearly all visible tumor, while the purpose of HIPEC is to eliminate microscopic residual disease.⁴ CRS+HIPEC has demonstrated significant improvements in the long-term survival of patients with peritoneal malignancy, particularly those with pseudomyxoma peritonei of appendiceal origin, peritoneal mesothelioma and locally advanced ovarian cancer.^{3,4}

Given the complexity of this procedure, it has been associated with high morbidity and mortality rates,³⁻⁵ and some centers adopted the policy of routine admission in intensive care units in the immediate postoperative period.^{6,7}

The primary aim of this study was to evaluate short-term outcomes after CRS+HIPEC regarding surgical morbidity, identify factors associated with selective ICU admission, and assess the safety of managing CRS+HIPEC patients outside of the ICU in a tertiary cancer center.

METHODS

A unicentric, retrospective, observational study of patients with peritoneal malignancy of various primaries submitted to CRS+HIPEC was conducted at Instituto Português de Oncologia do Porto (IPO-Porto). Surgeries performed between January 2016 and December 2020 were included. Patients who were only submitted to diagnostic laparotomy were excluded. IPO-Porto is a tertiary cancer center and a national referral center for CRS+HIPEC, performing approximately 60 procedures annually.

Patients' demographic and perioperative data were collected. Age, gender, classification according to American Society of Anesthesiologists (ASA) scale, and Eastern Cooperative Oncology Group (ECOG) Performance Status were analyzed. Operative details such as the extent and distribution of peritoneal malignancy measured by the Peritoneal Carcinomatosis Index (PCI), type of resection, estimated blood loss, duration of surgery and the Complete Cytoreduction Score (CC score) were all recorded.

1. SURGICAL MANAGEMENT

At our Institution, CRS+HIPEC was conducted following the protocol initially established by Sugarbaker.⁵ To ensure optimal visualization of the peritoneal cavity, a longitudinal incision extending from the xiphoid process to the pubic symphysis was consistently employed. Upon complete adhesiolysis, a comprehensive evaluation of tumor burden and peritoneal disease extent was performed, allowing for the calculation of the Peritoneal Cancer Index (PCI). The surgical intervention concluded with documentation of the quantity of peritonectomy procedures and visceral resections executed, as well as an assessment of the CC score.

Following tumor resection and before gastrointestinal tract reconstruction, HIPEC was administered for 60 minutes, with the intraperitoneal temperature maintained at 42°C. The chemotherapeutic regimen for HIPEC consisted of mitomycin C (20 mg/m²/2 L) in cases of appendiceal, colorectal, or

gastric primary malignancies, while cisplatin (50 mg/m²/2 L) was utilized for ovarian neoplasms and mesothelioma. The coliseum technique (open abdomen) was employed until April 2020, after which a transition to the closed abdomen method was implemented. All gastrointestinal anastomoses were performed following the completion of the HIPEC procedure.

In our institutional protocol, all patients are routinely admitted to the intermediate care unit post-operatively, while intensive care unit admission is reserved for selected cases based on clinical indication.

2. STATISTICAL ANALYSIS

Short-term outcomes were assessed, namely morbidity and mortality within 30 days postoperatively, which were classified according to the Common Terminology Criteria for Adverse Events (CTCAE). Descriptive statistics were presented using frequency tables for categorical variables and summary metrics (median and interquartile range [IQR] or mean and standard deviation [SD]) for continuous variables. Chi-squared test was used to identify differences between patients admitted to ICU. Multivariate analysis was conducted using logistic regression to identify prognostic factors associated with ICU admission. All factors clinically significant for ICU admission were used to build the logistic regression model. A *p*-value of <0.05 was considered statistically significant. Statistical analysis was made using IBM SPSS Statistics, version 28.

The study protocol received approval from the Ethics Committee of IPO-Porto. All data collected were anonymized and handled following the principles outlined in the Declaration of Helsinki.

RESULTS

Between January 2016 and December 2020, 259 surgeries were performed on 248 patients. The study population had a mean age of 58 years, with a predominance of female patients (n=179, 69.1%). Regarding physical status classification, the majority of patients were ASA II, with ASA III representing 32.8% of cases. Notably, 84.6% of patients presented with an ECOG Performance Status of 0. The mean pre-operative hemoglobin was 12.7 mg/dL and the mean pre-operative albumin was 2.7 g/dL. Of the 259 surgeries, in 87 (33.6%) the origin was appendicular, in 84 (32.4%) colorectal, in 40 (15.4%) ovarian, in 25 (9.7%) gastric, in 22 (8.5%) peritoneal and in one case (0.4%) the origin was the jejunum. All demographic and clinical characteristics of the patients, as well as the primary site of the peritoneal malignancy, are listed in detail in Table 1.

Table 1. Demographic and clinical characteristics of the patients submitted to CRS+HIPEC.

Variable	N	%
Gender		
Female	179	69.1%
Male	80	30.9%
ASA stage		
ASA II	174	67.2%
ASA III	85	32.8%
ECOG status		
ECOG 0	219	84.6%
ECOG 1	36	13.9%
ECOG 2	4	1.5%
Pre-op hemoglobin, mg/dL, mean	12.7	
Pre-op albumin, g/dL, mean	2.7	
Primary site		
Ileo-cecal appendix	87	33.6%
Colon and rectum	84	32.4%
Ovarian	40	15.4%
Stomach	25	9.7%
Peritoneum	22	8.5%
Jejunum	1	0.4%

Regarding surgical details, most of the surgeries (n=223, 86.1%) were performed through an open technique. The median PCI was 13. CC-0 was obtained in 78.3% of patients (n=191). The median operative time was 400 minutes, with a minimum of 243 and a maximum of 498 minutes. The median amount of blood loss during surgery was 200 mL. The median length of stay was 13 days. In 79.9% of surgeries (n=207), mitomycin C was the cytostatic agent used. The majority of patients (68.7%) had no complications, 22.8% had CT-CAE I/II complications, 7.7% had CT-CAE III/IV and two patients died (0.8%). The overall 30-day major morbidity rate was 8.7%. The operative parameters are listed in Table 2.

Table 2. Operative parameters.

Variable	N	%
HIPEC method		
Open	223	86.1
Closed	36	13.9
CC (n=244)		
CC-0	191	78.3
CC-1	34	13.9
CC-2	15	6.1
CC-3	4	1.6
Cytostatic agent		
Mitomycin C	207	79.9
Cisplatin	52	20.1
CT-CAE score		
CT-CAE 0	178	68.7
CT-CAE I/II	59	22.8
CT-CAE III/IV	20	7.7
CT-CAE V	2	0.8

Of the patients who presented morbidity after surgery (n=81, 31.3%), 43.2% (n=35) had medical complications and 56.8% (n=46) had surgical complications. The most common medical complications were pulmonary complications (atelectasis and pleural effusion); cardiovascular complications such as decompensated heart failure, and renal complications like acute renal failure and urinary tract infection. The majority of surgical complications were treated conservatively (71.8%, n=33). The most frequent surgical complications were intra-abdominal abscesses, all treated conservatively through imaging-guided drainage. Thirteen patients (5%) underwent re-operation, the majority due to anastomotic leak (n=8). The overall anastomotic leak rate was 3.1%.

One-third of patients, 33.6% (n=87), were admitted to the ICU for postoperative surveillance (<48 hours). Patients who were not admitted to ICU demonstrated similar overall morbidity to the patients admitted to ICU for <48 hours. These data are shown in Table 3.

Table 3 Overall morbidity and admission in ICU.

CT-CAE classification	No - ICU (n=172)	ICU (n=87)	p-value
No complications	121 (70.3%)	57 (65.6%)	0.407
GRADE 1/2	40 (23.3%)	19 (21.8%)	
GRADE 3/4	10 (5.8%)	10 (11.5%)	
GRADE 5	1 (0.6%)	1 (1.1%)	

Predictive factors for ICU admission (p<0.05) were PCI>13, intraoperative blood loss>200 mL and cytostatic agent cisplatin. There were no differences between groups regarding age, ASA, ECOG, gender or primary tumor (see Table 4).

Table 4 Multivariate analysis of prognostic factors for ICU admission.

	OR (95% CI)	p-value
PCI (>13)	3.116 (1.674-5.800)	<0.001
Blood loss (>200 mL)	2.419 (1.342-4.360)	0.003
Age (>60 years old)	0.900 (0.499-1.624)	0.727
ASA	1.072 (0.574-2.002)	0.827
ECOG (>0)	2.051 (0.945-4.449)	0.069
Gender (male)	0.831 (0.436-1.586)	0.576
Cytostatic agent	0.414 (0.177-0.966)	0.041
Primary tumor (non-appendiceal)	1.253 (0.633-2.479)	0.517

CI: confidence interval; OR: odds ratio

DISCUSSION

The combination of cytoreductive surgery and HIPEC led to a paradigm shift in the treatment and prognosis of patients with peritoneal disease, becoming the standard of care for several peritoneal surface malignancies.^{5,8} The present work aimed to present short-term outcomes and predictive factors for ICU admission in patients submitted to CRS+HIPEC. In our study, the overall 30-day morbidity rate was 31.3%, with severe morbidity (Grade III/IV) in 7.7% of patients and two deaths (0.8%). Patients admitted to the ICU <48h had similar short-term outcomes to the other patients, and only PCI, blood loss and the use of cisplatin were independent predictors of ICU admission.

Traditionally, CRS+HIPEC has been associated with high rates of postoperative morbidity, with previous studies presenting mortality rates ranging from 0%–17% and morbidity up to 60%.^{3–5} The exaggerated metabolic and inflammatory responses resulting from the surgical complexity of the procedure, coupled with the deleterious effects of heated chemotherapeutic agents on tissues, impact cardiovascular status, oxygen consumption, liver function, hematopoietic parameters, and electrolyte balance, potentially leading to life-threatening complications.^{1,9,10} These higher complication rates have led to the routine practice of postoperative admission to intensive care units, with the goal of prevention, as well as early detection and therapeutic intervention, in case of complications.^{6,7} Early intervention to reverse this pathophysiological cascade through improved perioperative care is a key focus of enhanced recovery after surgery (ERAS) protocols.¹¹ Adherence to ERAS protocols during the perioperative period has significantly reduced the incidence of grade III/IV complications, decreased ICU and hospital lengths of stay, and improved survival rates.^{1,11}

Contrary to earlier perceptions, contemporary data demonstrate that CRS+HIPEC is relatively safe, with reported morbidity rates around 30% and mortality rates between 0.9% and 5.8%, with most high-volume centers reporting mortality rates between 0% and 1%.^{1,3,12} When appropriate patients are selected, it has a similar risk profile compared to other major abdominal oncologic operations.^{1,2,4,12,13} Our results are in line with those described in the literature. Our overall morbidity rate was 31.3%, with 7.7% of major complications (CT-CAE III/IV), and our mortality was 0.8%. Our overall surgical complications rate was 17.7%, with just a 5% re-operation rate, suggesting that the conservative approach (applied in 12.7% of patients) was well tolerated. These data show that early detection of surgical complications is possible even without being admitted to an intensive care

unit. The overall anastomotic leak rate of 3%. Intra-abdominal abscesses were the most frequent complications, similar to what others have reported.^{4,14}

Current international literature has provided enough evidence that better patient selection, advancements in surgical techniques, improved perioperative management strategies, and the experience gained through the learning curve have all contributed to decreased morbidity and mortality in patients undergoing CRS+HIPEC.^{4,12} For that reason, we do not support routine admission to ICU post-operatively. In fact, in our series, only one-third of patients, 34.5% (n=87), were admitted to the ICU for postoperative surveillance (<48 hours) with similar overall morbidity when compared with the patients who were not admitted to ICU. There was no difference in minor morbidity (Grade I/II) between the two groups, while major morbidity (Grade III/IV) was slightly higher in the patients admitted to the ICU cohort. There was one case of mortality in each group.

Our results are in agreement with other studies that have shown that outcomes and mortality rates are similar between patients admitted to the ICU and those who are not.^{4,12} Several factors, including patient age, Eastern Cooperative Oncology Group (ECOG) performance status, nutritional status, biological behavior of the primary tumor, the completeness of cytoreduction, and the extent of peritoneal disease, play crucial roles in determining morbidity, mortality, and overall survival in these patients.^{9,13} In our series, PCI and intraoperative blood loss should be considered when deciding ICU admission as they were independent predictive factors for ICU admission. Notably, modifiable factors such as ASA score and ECOG status, did not influence ICU admission decisions, probably because most patients had undergone preoperative optimization.

Therefore, ICU admission should be evaluated on a case-by-case basis, considering the individual characteristics of the patient, their risk factors, and the extent of the surgical procedure, especially given that ICU care is a costly and limited resource.^{6,7,10}

This selective approach to ICU admission may optimize resource utilization and potentially reduce hospitalization costs for these complex cases.⁷ The Chicago Consensus Working Group on peritoneal surface malignancies recommends that CRS+HIPEC be performed at high-volume experienced centers.¹⁵ Our findings underscore the paramount importance of rigorous patient selection in achieving optimal postoperative outcomes in patients submitted to CRS+HIPEC.

The current study has several limitations. Firstly, it is a single-center, retrospective study, with its inherent selection bias. Second, the heterogeneity of the population, in terms of primary tumor type and PCI.

A notable strength of this study is the analysis of a large cohort of patients who present in this uncommon medical scenario at a single institution, with procedures performed by the same surgical and anesthesiological team. Furthermore, our two-decade institutional experience enabled the

development and implementation of a systematic protocol.

CONCLUSION

CRS-HIPEC is a complex procedure that can be performed with low morbidity and mortality. The findings of our study underscore that routine admission to the ICU does not seem to be necessary, which supports the current practice at our center of selective admission. This practice proves to be safe with potential implications for cost reduction.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

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CONTRIBUTORSHIP STATEMENT

SM: Conceptualization, formal analysis, investigation, methodology and writing of the original draft.

JM: Formal analysis, investigation, methodology, resources.

MP: Conceptualization, formal analysis, project administration, supervision, validation, visualization, writing, review and editing.

ML, FS, MF and AS: Validation, visualization, writing, review and editing.

All authors approved the final version to be published.

DECLARAÇÃO DE CONTRIBUIÇÃO

SM: Conceptualização, análise formal, investigação, metodologia e redação do projeto original.

JM: Análise formal, investigação, metodologia, recursos.

MP: Conceptualização, análise formal, administração do projeto, supervisão, validação, visualização, escrita, revisão e edição.

ML, FS, MF e AS: Validação, visualização, redação, revisão e edição.

Todos os autores aprovaram a versão final a ser publicada.

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